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(43) International Publication Date: 15 September 1994 (15.09.94)

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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and

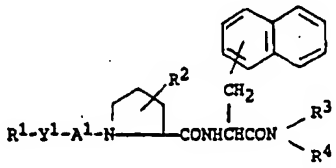
(75) Inventors/Applicants *(for US only)*: SONEOKA, Kunihiko [JP/JP]; 3-21-1-202, Yamadanishi, Suita-shi, Osaka 565 (JP). SHUTO, Hidetoshi [JP/JP]; 2-8-1-907, Kamihamuro, Takatsuki-shi, Osaka 569 (JP). FUJII, Takashi [JP/JP]; 2-2-13, Fushiodai, Ikeda-shi, Osaka 563 (JP).

(74) Agent: 7967 PATENT ATTORNEY SEKI HIDEO; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

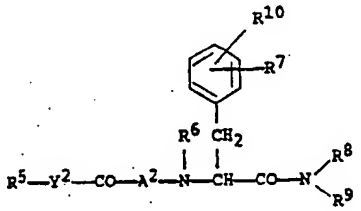
(54) Title: USE OF PEPTIDES FOR THE MANUFACTURE OF A MEDICAMENT

(57) Abstract

A use of peptide compounds of formula (I), (II) or (III) and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for preventing or treating chronic obstructive pulmonary diseases, iritis, psoriasis, inflammatory intestinal diseases, hepatitis, tenalgia attended to hyperlipidemia, postoperative neuroma, vulvar vestibulitis, hemodialysis-associated itching, lichen planus, laryngopharyngitis, bronchiectasis, coniosis whooping cough, pulmonary tuberculosis, emesis or mental diseases.



(I)



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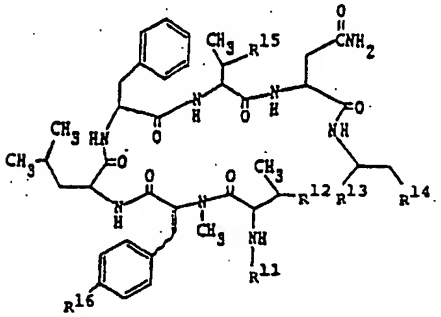

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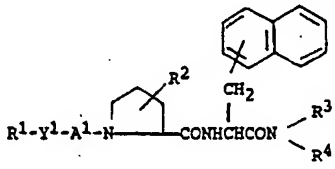
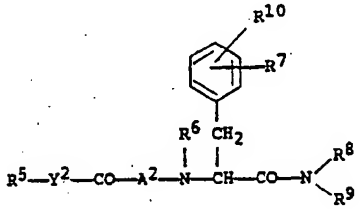


(I)



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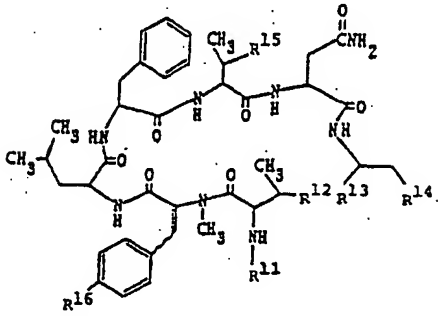

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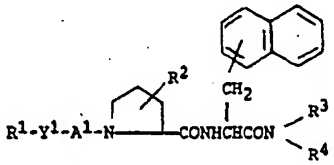

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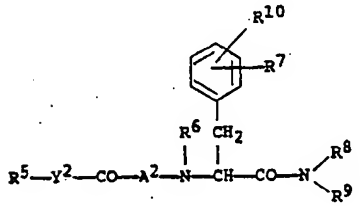

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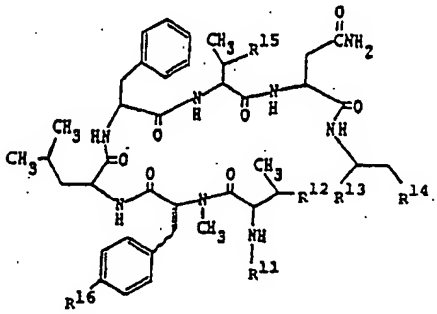

(III)

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USE OF PEPTIDES FOR THE MANUFACTURE OF A MEDICAMENT.

Technical Field :

This invention relates to a new use of peptide compounds. More specifically, this invention relates to a new use of peptide compounds for chronic obstructive pulmonary diseases, iritis, psoriasis, inflammatory intestinal diseases, hepatitis, tenalgia attended to hyperlipidemia, postoperative neuroma, vulvar vestibulitis, hemodialysis-associated itching, lichen planus, laryngopharyngitis, bronchiectasis, conoisis, whooping cough, pulmonary tuberculosis, emesis and mental diseases and the like.

Disclosure of the Invention :

Accordingly, this invention provides a new use of the peptide compounds for preventing or treating the diseases as mentioned above.

Further, this invention provides a prophylactic or therapeutic agent for the diseases as mentioned above, which comprises the peptide compounds.

Still further, this invention provides a method for preventing or treating the diseases as mentioned above, which comprises administering said peptide compounds to mammals.

Furthermore, this invention provides a pharmaceutical composition for preventing or treating the diseases as mentioned above, which comprises said peptide compounds, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

The compounds used in this invention are known to have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin

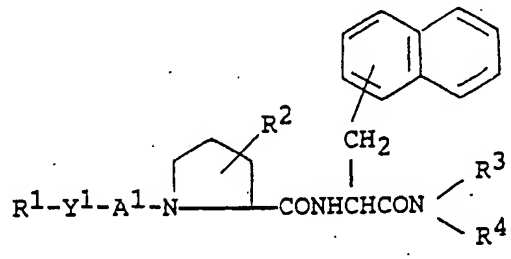
A antagonism or neurokinin B antagonism, and therefore are useful for treating or preventing tachykinin mediated diseases, particularly substance P mediated diseases such as asthma (e.g. European Publication No. 0 443 132 A1).

And the compounds used in this invention are expected to be used for treating bronchitis such as chronic bronchitis, acute bronchitis and diffuse panbronchilitis.

Further the compounds used in this invention exhibit analgesic action and are expected to be of use for treating various pains or aches such as migraine, headache, toothache, cancerous pain and back pain; and superficial pain on congelation, burn, herpes zoster or diabetic neuropathy.

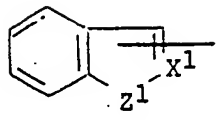
The inventors of this invention have found that the peptide compounds of this invention are also useful for the treatment of chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; tenalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; conoisis; whooping cough; pulmonary tuberculosis; emesis; or mental diseases, particularly anxiety and depression.

The peptide compounds used in the present invention can be represented by the following general formulae.

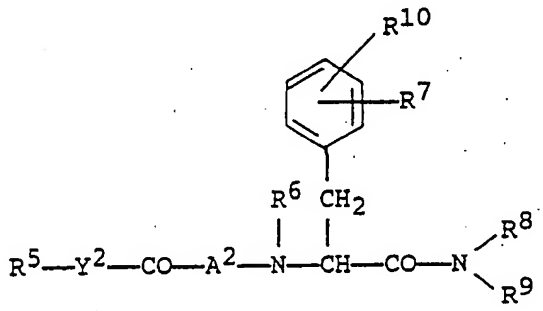


(I)

wherein R^1 is aryl, or a group of the formula :

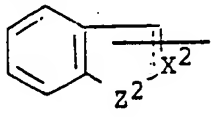


wherein X^1 is CH or N, and
Z^1 is O or N-R^{17},
in which R^{17} is hydrogen or lower alkyl,
R^2 is hydroxy or lower alkoxy,
R^3 is hydrogen or lower alkyl which may have suitable substituent(s),
R^4 is ar(lower)alkyl which may have suitable substituent(s),
A^1 is carbonyl or sulfonyl, and
Y^1 is bond or lower alkenylene,
and pharmaceutically acceptable salts thereof,



(II)

wherein R^5 is lower alkyl, aryl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :



wherein the symbol of a line and dotted line is a single bond or a double bond,

X^2 is CH or N, and

Z^2 is O, S or NH,

each of which may have suitable substituent(s);

R^6 is hydrogen or lower alkyl;

R^7 is suitable substituent;

R^8 is lower alkyl which may have suitable substituent(s), and

R^9 is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

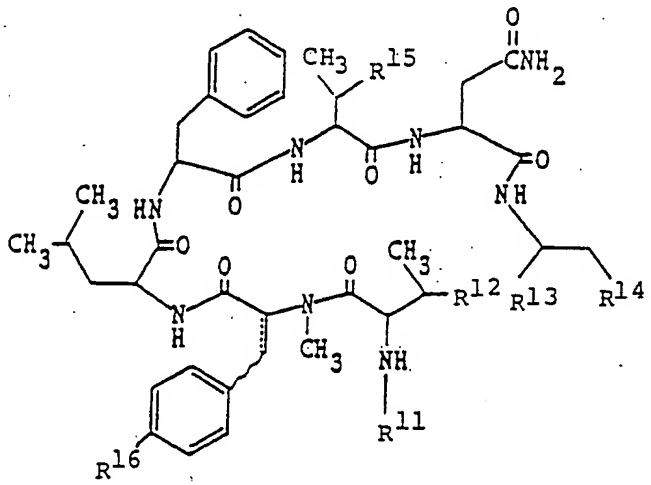
R^8 and R^9 are linked together to form benzene-condensed lower alkylene;

R^{10} is hydrogen or suitable substituent;

A^2 is an amino acid residue, which may have suitable substituent(s); and

Y^2 is bond, lower alkylene or lower alkenylene,

and pharmaceutically acceptable salts thereof, and



(III)

wherein R^{11} is hydrogen or an acyl group;

R^{12} is hydroxy and
R^{13} is carboxy or protected carboxy, or
R^{12} and R^{13} are linked together to represent a group of the formula : -O-C-; (O)

R^{14} is hydroxy or protected hydroxy;
R^{15} is hydroxy or protected hydroxy;
R^{16} is hydroxy, protected hydroxy or lower alkoxy; and
≡≡≡ is a single bond or a double bond,
and pharmaceutically acceptable salts thereof.

Suitable pharmaceutically acceptable salts of the starting and object compound are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

The suitable examples and illustrations of the various definitions used in the compounds of the formulae (I), (II) and (III) are explained in detail in the following.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise

indicated.

Suitable "lower alkyl" may include a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which the most preferred one is methyl.

Suitable "aryl" may include phenyl, tolyl, xylyl, mesityl, cumenyl, naphthyl, and the like, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl.

Suitable "lower alkenylene" is one having 2 to 6 carbon atom(s) and may include vinylene, propenylene, and the like, in which the preferred one is vinylene.

Suitable "lower alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of art such as lower alkyl as exemplified above, carboxy(lower)alkyl (e.g. carboxymethyl, carboxyethyl, etc.), protected carboxy(lower)alkyl such as esterified carboxy(lower)alkyl, for example, lower alkoxycarbonyl(lower)alkyl (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl, etc.), carbamoyl(lower)alkyl which may have suitable substituent(s) such as carbamoyl(lower)alkyl (e.g., carbamoylmethyl, carbamoylethyl, carbamoylpropyl, etc.) and carbamoyl(lower)alkyl having suitable substituent(s), for example, lower alkylcarbamoyl(lower)alkyl (e.g., methylcarbamoylmethyl, ethylcarbamoylmethyl, etc.), amino(lower)alkylcarbamoyl(lower)alkyl (e.g., aminomethylcarbamoylmethyl, aminoethylcarbamoylmethyl, etc.), lower alkylamino(lower)alkylcarbamoyl(lower)alkyl (e.g. dimethylaminomethylcarbamoylmethyl, dimethylaminomethylcarbamoylmethyl, etc.), lower alkylamino(lower)alkyl (e.g. dimethylaminomethyl, dimethylaminoethyl, etc.), hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, etc.), protected

hydroxy(lower)alkyl such as acyloxy(lower)alkyl, for example, lower alkanoyloxy(lower)alkyl (e.g. acetyloxyethyl, acetyloxypropyl, acetyloxybutyl, acetyloxypentyl, propionyloxymethyl, butyryloxymethyl, hexanoyloxymethyl, etc.), and the like.

Suitable "ar(lower)alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as ar(lower)alkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, etc.), substituted ar(lower)alkyl, for example, mono or di or trihalophenyl(lower)alkyl (e.g., o-fluorobenzyl, m-fluorobenzyl, p-fluorobenzyl, o-trifluoromethylbenzyl, etc.), and the like.

Suitable "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, hexyloxy, and the like.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene, ethylene or trimethylene.

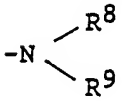
Suitable "an amino acid residue" means a bivalent residue derived from an amino acid, and such amino acid may be glycine (Gly), D- or L- alanine (Ala), ß-alanine (ßAla), D- or L- valine (Val), D- or L- leucine (Leu), D- or L- isoleucine (Ile), D- or L- serine (Ser), D- or L- threonine (Thr), D- or L- cysteine (Cys), D- or L- methionine (Met), D- or L- phenylalanine (Phe), D- or L- tryptophan (Trp), D- or L- tyrosine (Tyr), D- or L- proline (Pro), D- or L- didehydroproline (ΔPro) such as 3,4-didehydroproline (Δ(3,4)Pro), D- or L- hydroxypropine (Pro(OH)) such as 3-hydroxyproline (Pro(3OH)) and 4-hydroxyproline (Pro(4OH)), D- or L- azetidine-2-carboxylic acid (Azt), D- or L- thioproline (Tpr), D- or L- aminoproline ($Pro(NH_2)$) such as 3-aminoproline ($Pro(3NH_2)$)

and 4-aminoproline (Pro($4NH_2$)), D- or L- pyroglutamic acid (pGlu), D- or L- 2-aminoisobutyric acid (Aib), D- or L-glutamic acid (Glu), D- or L- aspartic acid (Asp), D- or L- glutamic (Gln), D- or L- asparagine (Asn), D- or L-lysine (Lys), D- or L- arginine (Arg), D- or L- histidine (His), D- or L- ornithine (Orn), D- or L-hydroxypiperidinecarboxylic acid such as 5-hydroxypiperidine-2-carboxylic acid, D- or L-mercaptoproline (Pro(SH)) such as 3-mercaptoproline (Pro(3SH)) and 4-mercaptoproline (Pro(4SH)), whose side chains are amino, hydroxy, thiol or carboxy groups, may be substituted by the suitable substituent(s). Said suitable substituent(s) may include acyl such as carbamoyl, lower alkanoyl (e.g., formyl, acetyl, etc.), trihalo(lower)alkoxycarbonyl (e.g. 2,2,2-trichloroethoxycarbonyl, etc.), ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), lower alkylsulfonyl (e.g., mesyl ethylsulfonyl, etc.), lower alkoxalyl (e.g., methoxalyl, ethoxalyl, etc.), arylsulfonyl (e.g., phenylsulfonyl, tolylsulfonyl, etc.), haloar(lower)-alkoxycarbonyl (e.g., o-chlorobenzyloxycarbonyl, etc.), carboxy(lower)alkanoyl (e.g., carboxyacetyl, carboxypropionyl, etc.), glycyl, ß-alanyl, N-lower alkoxycarbonylglycyl (e.g., N-t-butoxycarbonylglycyl, etc.) and N-lower alkoxycarbonyl-ß-alanyl (e.g., N-t-butoxycarbonyl-ß-alanyl, etc.), N,N-di(lower)alkylamino(lower)alkanoyl (e.g., N,N-dimethylaminoacetyl, N,N-diethylaminoacetyl, N,N-dimethylaminopropionyl, N,N-diethylaminopropionyl, etc.), carboxyalyl, morpholinocarbonyl, amino(lower)alkanoyl (e.g., aminoacetyl, aminopropionyl, etc.), N-ar(lower)alkoxycarbonylamino(lower)alkanoyl (e.g., N-benzyloxycarbonylaminoacetyl, etc.), threonyl, N-lower alkoxycarbonylthreonyl (e.g. N-t-butoxycarbonylthreonyl, etc.), N-lower

alkanoylthreonyl (e.g., N-acetylthreonyl, etc.), N-lower alkoxycarbonyl(lower)alkyl-N-lower alkoxycarbonylamino(lower)alkanoyl (e.g., N-t-butoxycarbonylmethyl-N-t-butoxycarbonylaminoacetyl, etc.), α-glutamyl, N-ar(lower)alkoxycarbonyl-O-ar(lower)alkyl-α-glutamyl (e.g., N-benzyloxycarbonyl-O-benzyl-α-glutamyl, etc.), γ-glutamyl, N-ar(lower)alkoxycarbonyl-O-ar(lower)alkyl-γ-glutamyl (e.g., N-benzyloxycarbonyl-O-benzyl-γ-glutamyl, etc.), lower alkyl (e.g., methyl, ethyl, t-butyl, etc.), carboxy(lower)alkyl (e.g. carboxymethyl, etc.), morpholino, glycine amide, threonino amide, N'-glutamino N-lower alkylamide (e.g., N'-glutamino N-t-butylamide, etc.), di(lower)alkylamino (e.g. dimethylamino, etc.), ar(lower)alkyl (e.g., benzyl, phenethyl, etc.), trihalo(lower)alkyl (e.g., 2,2,2-trichloroethyl, etc.), lower alkoxycarbonyl(lower)alkyl (e.g., methoxycarbonylmethyl, ethoxycarbonylmethyl, t-butoxycarbonylmethyl, etc.), or usual protecting group used in the field of art. In case that such amino acid contain a thio, it may be its sulfoxide or sulfone.

Suitable "pyridyl(lower)alyl" may include 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, and the like.

Suitable group of the formula :



, in which R^8 and R^9 are linked together to form benzene-condensed lower alkylene, may include 1-indolinyl, 2-isoindolinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, and the like.

Suitable substituent on R^5 moiety may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as lower alkyl which may have suitable substituent(s), amino protective group, each as defined above, hydroxy, halogen (e.g. fluoro, chloro,

etc.), lower alkoxy (e.g. methoxy, butoxy, etc.), N,N-di(lower)alkylamino (e.g. dimethylamino, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, t-butoxycarbonyl, etc.), and the like.

Suitable substituent for R^7 and R^{10} may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as lower alkyl which may have suitable substituent(s) as mentioned above, carboxy(lower)alkoxy, protected carboxy(lower)alkoxy, each as defined above, halogen (e.g. fluoro, chloro, etc.), hydroxy, lower alkoxy (e.g. methoxy, butoxy, etc.), nitro, amino, protected amino, in which amino protective group is as defined above, and the like.

The term "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise indicated.

Suitable "acyl" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :-

Aliphatic acyl such as lower or higher alkanoyl (e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);
lower or higher alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);
lower or higher alkanesulfonyl (e.g. methanesulfonyl,

ethanesulfonyl, etc.);
lower or higher alkoxysulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g. benzoyl, toluoyl, naphthoyl, etc.);

ar(lower)alkanoyl [e.g. phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g. naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g. phenyl(lower)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl, naphthylpentenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl [e.g. phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), etc.];
aryloxycarbonyl (e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc.);
aryloxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.);
arylglyoxyloyl (e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.);
arenesulfonyl (e.g. benzenesulfonyl, p-toluenesulfonyl, etc.); or the like;

Heterocyclic acyl such as

heterocycliccarbonyl (e.g. thenoyl, furoyl, nicotinoyl, etc.);
heterocyclic(lower)alkanoyl (e.g. thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl, tetrazolylacetyl, etc.);
heterocyclicglyoxyloyl (e.g. thiazolylglyoxyloyl, thienylglyoxyloyl, etc.); or the like; in which suitable heterocyclic moiety in the terms "heterocycliccarbonyl",

"heterocyclic(lower)alkanoyl" and "heterocyclicglyoxyloyl" as mentioned above means, in more detail, saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;
unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc. and the like.

The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s) such as lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.);
lower alkenyl (e.g. vinyl, allyl, 1-propenyl, 1 or 2 or 3-

butenyl, 1 or 2 or 3 or 4-pentenyl, 1 or 2 or 3 or 4 or 5-hexenyl, etc.);
lower alkoxy (e.g. methoxy, ethoxy, propoxy, etc.);
lower alkylthio (e.g. methylthio, ethylthio, etc.);
lower alkylamino (e.g. methylamino, etc.);
cyclo(lower)alkyl (e.g. cyclopentyl, cyclohexyl, etc.);
cyclo(lower)alkenyl (e.g. cyclohexenyl, etc.);
halogen; amino; protected amino; hydroxy; protected hydroxy; cyano; nitro; carboxy; protected carboxy; sulfo; sulfamoyl; imino; oxo; amino(lower)alkyl (e.g. aminomethyl, aminoethyl, etc.);
carbamoyloxy; hydroxy(lower)alkyl (e.g. hydroxymethyl, 1 or 2-hydroxyethyl, 1 or 2 or 3-hydroxypropyl, etc.);
cyano(lower)alkenylthio (e.g. cyanovinylthio, etc.);
or the like.

Suitable "hydroxy protective group" in the term "protected hydroxy" may include phenyl(lower)alkyl (e.g. benzyl, etc.), acyl as mentioned above, and the like.

Suitable "protected carboxy" may include esterified carboxy.

Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester,

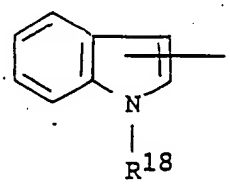
1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.], lower alkanesulfonyl-(lower)alkyl ester (e.g. 2-mesylethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl ester (e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyl-oxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), phthalidylidene(lower)alkyl ester, or (5-lower alkyl 2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];
lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.);
lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.);
ar(lower)alkyl ester which may have at least one suitable substituent(s) such as mono(or di or tri)phenyl(lower)-alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.);
aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.);
phthalidyl ester; and the like.

Particularly, the preferred embodiments of R^1, R^2, R^3, R^4, A^1 and Y^1 are as follows.

R^1 is phenyl;
benzofuryl;
indazolyl; or
indolyl (e.g. 1H-indol-3-yl, etc.);
1-lower alkyl indolyl (e.g. 1-methyl-1H-indol-2-yl, 1-methyl-1H-indol-3-yl, 1-isopropyl-1H-indol-3-yl, etc.),
R^2 is hydroxy; or
lower alkoxy (e.g. methoxy, etc.),
R^3 is hydrogen;
lower alkyl (e.g. methyl, etc.); or
hydroxy(lower)alkyl (e.g. hydroxymethyl, hydroxyethyl, etc.),
R^4 is phenyl(lower)alkyl (e.g. benzyl, phenethyl, etc.);
or halophenyl(lower)alkyl (e.g. o-fluorobenzyl, m-fluorobenzyl, p-fluorobenzyl, etc.);
A^1 is carbonyl; or
sulfonyl, and
Y^1 is bond; or
lower alkenylene (e.g. vinylene, etc.).

Particularly, the preferred embodiments of R^5, R^6, R^7, R^8, R^9, R^{10}, A^2 and Y^2 are as follows.

R^5 is aryl such as phenyl and naphthyl, which may have one or more, preferably one to three halogen or lower alkoxy (e.g. phenyl, difluorophenyl, dimethoxyphenyl, etc.);
benzofuryl;
pyridyl;
or a group of the formula :



wherein R^{18} is hydrogen; or
lower alkyl (e.g. methyl, etc.);
R^6 is hydrogen; or
lower alkyl (e.g. methyl, etc.);
R^7 is lower alkyl which may have one or more, preferably one to three halogen (e.g. methyl, trifluoromethyl, etc.);
amino;
acylamino such as lower alkanesulfonylamino (e.g. methanesulfonylamino, etc.);
carboxy(lower)alkoxy (e.g. carboxymethoxy, etc.);
esterified carboxy(lower)alkyl such as lower alkoxycarbonyl(lower)alkoxy (e.g. ethoxycarbonylmethoxy, etc.);
halogen (e.g. fluoro, chloro, etc.);
lower alkoxy (e.g. methoxy, etc.); or
nitro;
R^8 is lower alkyl (e.g. methyl, etc.);
R^9 is ar(lower)alkyl such as mono or di or triphenyl(lower)alkyl, preferably phenyl(lower)alkyl (e.g. benzyl, etc.);
R^{10} is hydrogen;
lower alkyl (e.g. methyl, etc.); or
halogen (e.g. chloro, etc.);
A^2 is a bivalent residue derived from an amino acid, which may have suitable substituent(s) such as hydroxyproline (e.g. 4-hydroxyproline, etc.); or didehydroproline (e.g. 3,4-didehydroproline, etc.); and
Y^2 is bond;
lower alkylene (e.g. ethylene, etc.); or
lower alkenylene (e.g. vinylene, etc.).

Particularly, the preferred embodiments of R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are as follows.

R^{11} is hydrogen, ar(lower)alkoxycarbonyl (more preferably phenyl(lower)alkoxycarbonyl), lower alkanoyl, higher alkanoyl (more preferably C_{15}-C_{20} alkanoyl), aroyl (more preferably benzoyl), heterocyclic(lower)alkanoyl (more preferably thienyl(lower)alkanoyl), ar(lower)alkenoyl substituted with a lower alkenyl group (more preferably phenyl(lower)alkenoyl substituted with a lower alkenyl group), or ar(lower)alkanoyl substituted with a lower alkyl group (more preferably phenyl(lower)alkanoyl substituted with a lower alkyl group);

R^{12} is hydroxy and

R^{13} is carboxy or esterified carboxy (more preferably lower alkoxycarbonyl), or

R^{12} and R^{13} are linked together to represent a group of the formula : -O-C- ;
‖
O

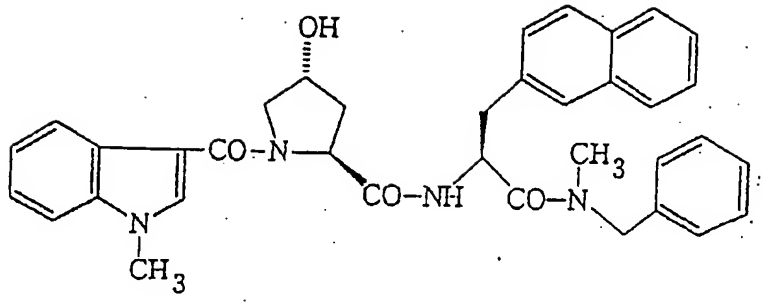
R^{14} is hydroxy, ar(lower)alkoxy (more preferably phenyl(lower)alkoxy) or acyloxy (more preferably lower alkanoyloxy);

R^{15} is hydroxy, ar(lower)alkoxy (more preferably phenyl(lower)alkoxy) or acyloxy (more preferably lower alkanoyloxy);

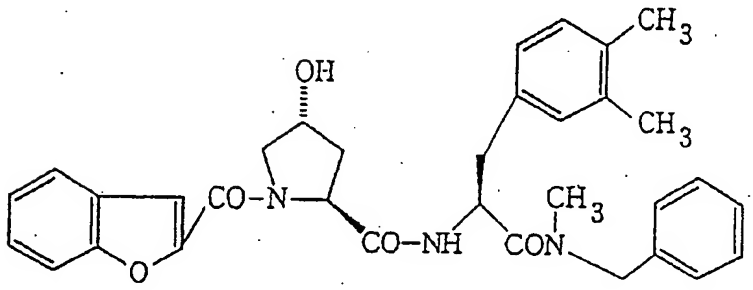
R^{16} is hydroxy, lower alkoxy, ar(lower)alkoxy (more preferably phenyl(lower)alkoxy) or acyloxy (more preferably lower alkanoyloxy); and

=== is a single bond or a double bond.

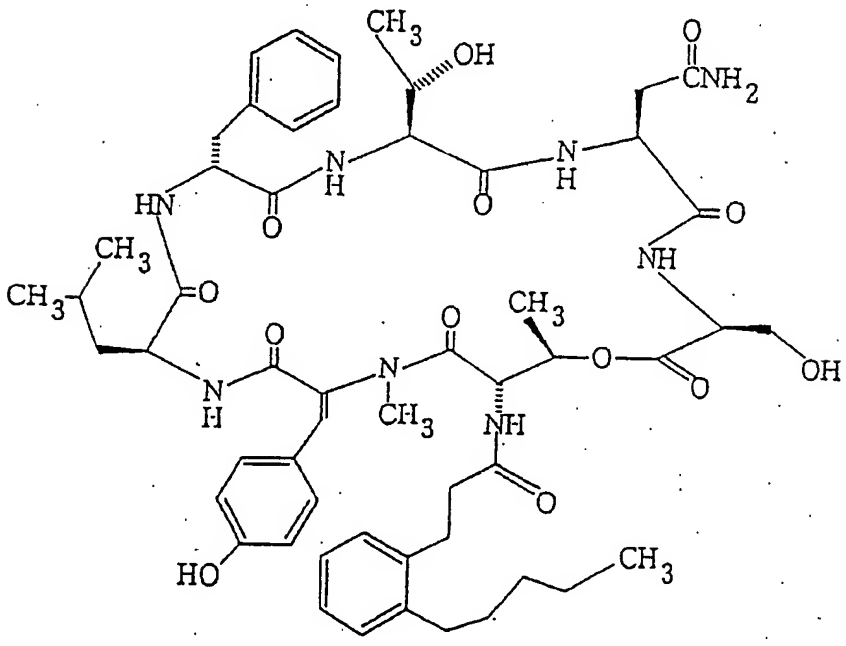
Further, the most interesting compounds are the compounds A, B and C of the following formulae.



(Compound A)



(Compound B)



(Compound C)

The compounds of the general formulae (I), (II) and (III), and the specific compounds mentioned above are known compounds, and the methods for preparation thereof are described, for example, in the following publications, or they can be prepared by a conventional method.

European Patent Publication 0 443 132 A2
European Patent Publication 0 482 539 A2
European Patent Publication 0 336 230 A2
International Publication WO 93/21215

The peptide compounds of the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the peptide compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external including topical, enteral, intravenous, intramuscular, parenteral, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, suppositories, solutions (saline, for example), emulsion, suspension (olive oil, for example), lotions, creams, ointment, dragees, granules, powder, injection, cataplasm, gel, tape, ophthalmic solutions, syrup, aerosol, and other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations,

in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by oral, parenteral, external (topical), enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration.

While the dosage of therapeutically effective amount of the peptide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg of the active ingredient is generally given for treating diseases, and an average single dose of about 0.1 mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

The following examples are given for the purpose of illustrating the present invention.

Example 1

Compound A	1 mg
Lactose	39 mg
total	40 mg

Example 2

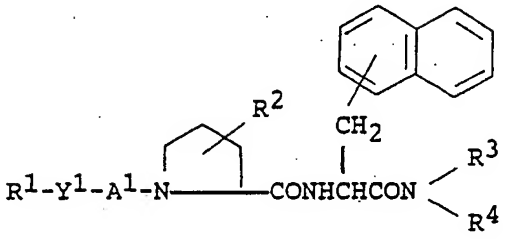
Compound B		1 mg
Lactose		39 mg
	total	40 mg

Example 3

Compound C		1 mg
Lactose		39 mg
	total	40 mg

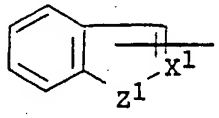
CLAIMS

1. A use of peptide compounds of the formula :

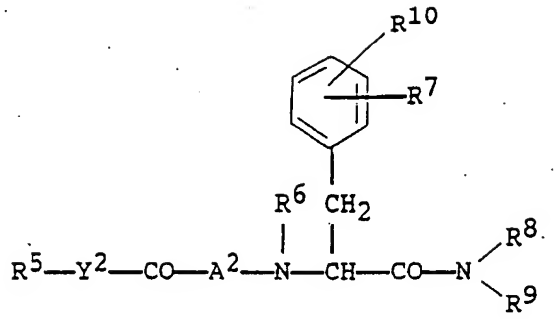


(I)

wherein R^1 is aryl, or a group of the formula :

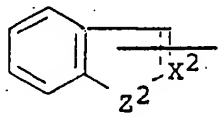


wherein X^1 is CH or N, and
Z^1 is O or N-R^{17},
in which R^{17} is hydrogen or lower alkyl,
R^2 is hydroxy or lower alkoxy,
R^3 is hydrogen or lower alkyl which may have suitable substituent(s),
R^4 is ar(lower)alkyl which may have suitable substituent(s),
A^1 is carbonyl or sulfonyl, and
Y^1 is bond or lower alkenylene,
and pharmaceutically acceptable salts thereof,



(II)

wherein R^5 is lower alkyl, aryl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :



wherein the symbol of a line and dotted line is a single bond or a double bond,

X^2 is CH or N, and

Z^2 is O, S or NH,

each of which may have suitable substituent(s);

R^6 is hydrogen or lower alkyl;

R^7 is suitable substituent;

R^8 is lower alkyl which may have suitable substituent(s), and

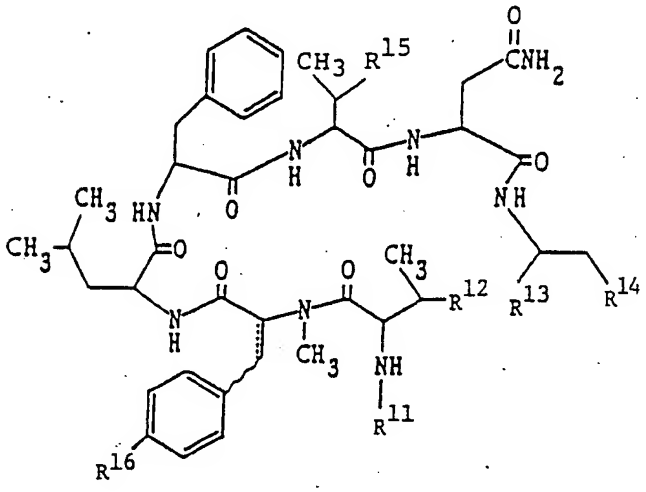
R^9 is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

R^8 and R^9 are linked together to form benzene-condensed lower alkylene;

R^{10} is hydrogen or suitable substituent;

A^2 is an amino acid residue, which may have

suitable substituent(s); and
Y^2 is bond, lower alkylene or lower alkenylene,
and pharmaceutically acceptable salts thereof, or



(III)

wherein R^{11} is hydrogen or an acyl group;
R^{12} is hydroxy and
R^{13} is carboxy or protected carboxy, or
R^{12} and R^{13} are linked together to represent a group of the formula : -O-C(=O)- ;
R^{14} is hydroxy or protected hydroxy;
R^{15} is hydroxy or protected hydroxy;
R^{16} is hydroxy, protected hydroxy or lower alkoxy; and
=== is a single bond or a double bond,
and pharmaceutically acceptable salts thereof,
for the manufacture of a medicament for preventing or treating chronic obstructive pulmonary diseases, iritis, psoriasis, inflammatory intestinal diseases,

hepatitis, tenalgia attended to hyperlipidemia, postoperative neuroma, vulvar vestibulitis, hemodialysis-associated itching, lichen planus, laryngopharyngitis, bronchiectasis, conoisis, whooping cough, pulmonary tuberculosis, emesis or mental diseases.

2. A use of claim 1 of the compound (I) defined in claim 1.

3. A method for preventing or treating chronic obstructive pulmonary diseases, iritis, psoriasis, inflammatory intestinal diseases, hepatitis, tenalgia attended to hyperlipidemia, postoperative neuroma, vulvar vestibulitis, hemodialysis-associated itching, lichen planus, laryngopharyngitis, bronchiectasis, conoisis, whooping cough, pulmonary tuberculosis, emesis or mental diseases, which comprises administering the compound (I), (II) or (III) defined in claim 1 to mammals.

4. A method of claim 3 which comprises administering the compound (I) defined in claim 1 to mammals.

5. A pharmaceutical composition for preventing or treating chronic obstructive pulmonary diseases, iritis, psoriasis, inflammatory intestinal diseases, hepatitis, tenalgia attended to hyperlipidemia, postoperative neuroma, vulvar vestibulitis, hemodialysis-associated itching, lichen planus, laryngopharyngitis, bronchiectasis, conoisis, whooping cough, pulmonary tuberculosis, emesis or mental diseases, comprising a compound (I), (II) or (III) defined in claim 1, as an active ingredient, in association with a pharmaceutically acceptable,

substantially non-toxic carrier or excipient.

6. A pharmaceutical composition of claim 5 comprising the compound (I) defined in claim 1 as an active ingredient.

7. A use of the compound (I), (II) or (III) defined in claim 1 for preventing or treating chronic obstructive pulmonary diseases, iritis, psoriasis, inflammatory intestinal diseases, hepatitis, tenalgia attended to hyperlipidemia, postoperative neuroma, vulvar vestibulitis, hemodialysis-associated itching, lichen planus, laryngopharyngitis, bronchiectasis, conoisis, whooping cough, pulmonary tuberculosis, emesis or mental diseases.

8. A use of claim 7 of the compound (I) defined in claim 1.

Inter. nal Application No
PCT/JP 94/00285

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 400 637 (FUJISAWA PHARMACEUTICAL CO) 5 December 1990 see page 2, line 19 - page 3, line 52	1,3,5,7
X	EP,A,0 443 132 (FUJISAWA PHARMACEUTICAL CO) 28 August 1991 cited in the application see page 3, line 1 - line 52 see page 11, line 51 - page 12, line 17	1-8
X	EP,A,0 482 539 (FUJISAWA PHARMACEUTICAL CO) 29 April 1992 cited in the application see page 3, line 1 - line 57 see page 21, line 25 - line 49	1,3,5,7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 June 1994	15 -06- 1994

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Rempp, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 94/00285

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 336 230 (FUJISAWA PHARMACEUTICAL CO) 11 October 1989 cited in the application see page 3, line 1 - line 49 see page 33, line 41 - page 36, line 19	1,3,5,7
X,P	WO,A,93 21215 (FUJISAWA PHARMACEUTICAL CO) 28 October 1993 cited in the application see page 1, line 5 - page 3, line 4 see page 13, line 26 - page 15, line 4	1,3,5,7

INTERNATIONAL SEARCH REPORT | PCT/JP 94/00285

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claims 3,4,7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/JP 94/00285

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		DE-T-	69004151	24-03-94
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